DEC 2 2 2006

510(k) Summary

K063543

Introduction

Roche Diagnostics Corporation hereby submits this Bundled Special 510(k): Device Modification to provide notification of modifications to our Bilirubin (Total and Direct) test systems. The reagents were originally cleared for use as:
COBAS INTEGRA Bilirubin Direct K951595
COBAS INTEGRA Total Bilirubin Special K981632/A001
Roche/Hitachi Total Bilirubin K981632/A001

Note that COBAS INTEGRA Total Bilirubin Special and Roche/Hitachi Total Bilirubin are different applications of the exact same reagent.

Modifications to the test systems include:
Device 1: COBAS INTEGRA Bilirubin Direct

- Changes to the traceability
- In the Limitations section, quantification of lipemia and hemolysis interference, rather than a statement to avoid lipemia and hemolyzed specimens
- Clarification for reagent handling
- Change to pH value for R1 from 1.1 to 1.2
- Change in stated lower detection limit from 0.81 µmol/L to 1.7 µmol/L. The change is due to Roche's decision to redefine the lower detection limit for clinical chemistry test systems to match the lower end of the measuring range even if data support a lower detection limit. This does not represent a change in actual performance; but rather only a change in the stated performance claim.
- Change in recommended calibrator to the Calibrator for Automated systems (C.f.a.s.) cleared by FDA under 510(k) K062319
- Other editorial labeling changes

Device 2: COBAS INTEGRA Total Bilirubin Special K981632/A001

- Modifications to specimen collection
- Labeling changes – addition of two clarifying statements in the Specimen collection and preparation section: "Do not use cordblood samples" and "Underfilled lithium heparin sample tubes may cause elevated results"
- Other editorial labeling changes

Continued on next page

510(k) Summary – Calibrator for Automated Systems (C.f.a.s), Continued

Introduction (continued)

Device 3: Roche/Hitachi Total Bilirubin K981632/A001

- Modifications to specimen collection section to include clarification that underfilled lithium heparin sample tubes may cause elevated results
- Clarification for reagent handling
- Labeling changes – Addition of two clarifying statements in the Specimen collection and preparation section: "Do not use cordblood samples" and "Underfilled lithium heparin sample tubes may cause elevated results"
- Other editorial labeling changes

Submitter name, address, contact

Roche Diagnostics
9115 Hague Rd
Indianapolis IN 46250
(317) 521-3723

Contact person: Corina Harper

Date prepared: October 30, 2006

Device Name

Device 1:
Proprietary name: COBAS INTEGRA Bilirubin Direct
Common name: Bilirubin Direct
Classification name: Bilirubin (total or direct) test system

Device 2:
Proprietary name: COBAS INTEGRA Total Bilirubin Special
Common name: Total Bilirubin
Classification name: Bilirubin (total or direct) test system

Device 3:
Proprietary name: Roche/Hitachi Total Bilirubin
Common name: Total Bilirubin
Classification name: Bilirubin (total or direct) test system

Establishment registration

The establishment registration number for Roche Diagnostics Gmbh Penzberg is 9610529.

The establishment registration number for Roche Diagnostics Corporation Indianapolis is 1823260.

Classification

The FDA has classified Bilirubin (total or direct) test system in Class II.

Panel	Classification Number	Classification Name	Regulation Citation
75 Clinical Chemistry	CIG	Bilirubin (total or direct) test system	21 CFR 862.1110

Device Description

The COBAS INTEGRA and Roche/Hitachi total or direct reagent is intended for use on the COBAS INTEGRA and Roche/Hitachi systems for the quantitative determination of total or direct bilirubin in serum and plasma.

Intended use

Device 1: COBAS INTEGRA Bilirubin Direct:
The cassette COBAS INTERGA Bilirubin Direct contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative determination of the direct (conjugated) bilirubin concentration in serum and plasma. .

Device 2: COBAS INTEGRA Total Bilirubin Special:
The COBAS INTERGA Total Bilirubin Special cassette contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative determination of total bilirubin in serum and plasma of adults and neonates.

Device 3: Roche/Hitachi Total Bilirubin:
For the quantitative determination of total bilirubin in serum and plasma of adults and neonates on Roche/Hitachi automated clinical chemistry analyzers.

Predicate Device

We claim substantial equivalence to
Device 1: Bilirubin Direct cleared as K951595
Device 2: Total Bilirubin cleared as K981632/A001
Device 3: Total Bilirubin cleared as K981632/A001

Continued on next page

510(k) Summary – Calibrator for Automated Systems (C.f.a.s), Continued

Substantial equivalency – Similarities

The table below indicates the similarities and differences between the modified Bilirubin direct or total reagents and their predicate devices.

Feature	Predicate device: **Device 1: COBAS INTEGRA Bilirubin Direct K951595** **Device 2: COBAS INTEGRA Total Bilirubin Special K981632/A001** **Device 3: Roche/Hitachi Total Bilirubin K981632/A001**	Modified device: **COBAS INTEGRA Bilirubin Direct** **COBAS INTEGRA Total Bilirubin Special** **Roche/Hitachi Total Bilirubin**
General		
Intended Use/ Indications for Use	Device 1: COBAS INTEGRA Bilirubin Direct The cassette COBAS INTEGRA Bilirubin Direct (BIL-D) contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative determination of the direct (conjugated) bilirubin concentration in serum and plasma (test BIL-D, 0-049). Device 3: COBAS INTEGRA Total Bilirubin Special The COBAS INTEGRA Total Bilirubin Special (BILTS) cassette contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative determination of total bilirubin in serum and plasma of adults and neonates (test BILTS, 0-985). Roche Hitachi Total Bilirubin Special For the quantitative determination of total bilirubin in serum and plasma of adults and neonates on Roche/Hitachi automated clinical chemistry analyzers.	Same Same Same

Specimen	Device 1: serum and plasma Device 2: serum and plasma of adults and neonates Device 3: serum and plasma of adults and neonates	Same Same Same
Test Principle		
Reference method	Device 1: Diazo method Device 2: Diazo method Device 3: Diazo method	Same Same Same
Reagent information		
Reagent composition	Device 2: COBAS INTEGRA Total Bilirubin Special R1: Sodium acetate buffer 85 mmol/L, Sulfamic acid 110 mmol/L R2: Hydrochloric acid 100 mmol/L, Diazonium ion 3 mmol/L Device 3: Roche/Hitachi Total Bilirubin R1: Sodium acetate buffer 85 mmol/L, Sulfamic acid 110 mmol/L R2: Hydrochloric acid 100 mmol/L, Diazonium ion 3 mmol/L	Same Same
Stability - shelf life and on-board	Device 1: 15-25 °C until expiration date On-board at 8 °C 12 weeks Device 2: 2-8 °C until expiration date COBAS INTEGRA 700 On-board at 8 °C 5 weeks Device 3: 2-8 °C until expiration date 35 days opened and refrigerated on the analyzer	15-25 °C until expiration date COBAS INTEGRA 400/400 plus: On-board at 10-15 °C 8 weeks COBAS INTEGRA 700/800: On-board at 8 °C 12 weeks 2-8 °C until expiration date COBAS INTEGRA 400/400 plus: On-board at 10-15 °C 5 weeks COBAS INTEGRA 700/800: On-board at 8 °C 5 weeks Same

Calibrator	Device1: Calibrator (human) Device 2: Calibrator f.a.s. Device 3: Calibrator f.a.s.	Calibrator f.a.s. Same Same
Quality control	Device1: Control Serum N Control Serum P Device 2: Precinorm U, Precipath U Precinorm U plus, Precipath U plus Device 3: Precinorm U, Precipath U Precitrol N, Precitrol A,	Precinorm U, Precipath U Precinorm U plus, Precipath U plus, Same Precinorm U, Precipath U Precinorm U plus, Precipath U plus
Traceability	Device 2: Standardized against the Doumas reference method Device 3: Standardized against the Doumas reference method	Same Same
Performance characteristics		

Precision	Device1: Within run: 1.7% @ 6.1 µmol/L 0.53% @ 20.1 µmol/L Between day: 1.1% @ 6.1 µmol/L 1.1% @ 20.1 µmol/L Total: 1.9% @ 6.1 µmol/L 1.2% @ 20.1 µmol/L Device 2: Within run: 2.44% @ 15.80 µmol/L 1.39% @ 54.00 µmol/L Between day: 4.13% @ 14.7 µmol/L 2.15% @ 47.20 µmol/L Device 3: Within run: 0.4% @ 18.53 mg/dL 2.8% @ 0.91mg/dL Between day: 2.5% @ 18.08 mg/dL 4.9% @ 0.89 mg/dL	Same Within run and total CV% reported Same Within run: 0.81% @ 18.81 mg/dL 3.1% @ 0.87 mg/dL Between day: 0.83% @ 15.41 mg/dL 2.2 % @ 0.86 mg/dL
Measuring range	Device1: 0-20 mg/dL Device 2: 0-25 mg/dL 0-250 mg/dL (with postdulion) Device 3: 0.1-35.0 mg/dL	0.10-25 mg/dL 0-25 mg/dL 0-100 mg/dL (with postdulion) Same

Lower detection limit	Device1: 3.1 x 10^{-3} ΔA per mg/dL of direct bilirubin Device 2: 0.063 mg/dL Device 3: 0.1 mg/dL	0.10 mg/dL Same Same
Expected values (literature reference)	Device1: Serum 0-0.2 mg/dL Device 2 and 3: Adults and children: up to 1.0 mg/dL Neonates: Age of newborn Premature 24hrs: 1.0-6.0 mg/dL 48hrs: 6.0-8.0 mg/dL 3-5 days: 10.0-15.0 mg/dL Age of newborn Full Term 24hrs: 2.0-6.0 mg/dL 48hrs: 6.0-7.0 mg/dL 3-5 days: 4.0-12.0 mg/dL	Same Same for Device 2 and 3
Endogenous interferences	Device 3: Serum and Plasma: Hemolysis: no significant interferences up to an H index of 1000 Lipemia: • significant negative interferences at an L index greater than 600 (on Hitachi 704,717,914,736,737,747) • No sifnificant interference up to an L index of 1000 (on Hitachi 902,911, 912, 917)	Same N/A – assay not offered on this instruments Same
Exogenous interferences	Device 2: Ascorbic acid at 30 mg/dL causes artificially decresed total bilirubin values Device 3: Indican: no significant interferences up to levels of 10 mg/dL	Same Same

510(k) Summary – Calibrator for Automated Systems (C.f.a.s), Continued

Substantial Differences

The table below indicates the differences between the modified Bilirubin direct or total reagents and their predicate devices.

Feature	Predicate device: **COBAS INTEGRA Bilirubin Direct K951595** **COBAS INTEGRA Total Bilirubin Special K981632/A001** **Roche/Hitachi Total Bilirubin K981632/A001**	Modified device: **COBAS INTEGRA Bilirubin Direct** **COBAS INTEGRA Total Bilirubin Special** **Roche/Hitachi Total Bilirubin**
Reagent information		
Reagent composition	Device 1: COBAS INTEGRA Bilirubin Direct R1: Sulfanic acid 35 mmol/L, Oxalic acid 40 mmol/L, HEDTA 4.0 mmol/L, pH 1.1 R2: Sodium nitrite 3.9 mmol/L, pH 6.0	R1: Sulfanic acid 35 mmol/L, Oxalic acid 40 mmol/L, HEDTA 4.0 mmol/L, pH 1.2 Same
Traceability	Device 1: Standardized against the manual test performance using the Jendrassic Grof method	Standardized against the Doumas reference method
Endogenous interferences	Device1: Hemolysis: even slight hemolysis interferes with the test Lipemia: : even slight lipemia interferes with the test Device 2: Hemolysis: No significant interference up to 1000 mg/dL Lipemia: No significant interference up to 1800 mg/dL as Intralipid	Hemolysis: No significant interference up to an H index of 10 Lipemia: No significant interference up to an L index of 270 Hemolysis: No significant interference up to 1000 mg/dL Lipemia: No significant interference up to 1400 mg/dL as Intralipid

Additional information for modifications to values assignment process and traceability	Direct Bilirubin: Roche Diagnostics has revised the calibration of the COBAS INTEGRA Bilirubin Direct method due to ongoing quality assurance and customer feedback. Traceability was changed to the Doumas method, and the concurrent change in Quality Control limits for this method were intended to minimize or eliminate any discrepancies seen by the users. The impact of using new setpoints was shift to direct bilirubin values lower when compared to the values obtained using previous setpoints. The shift occurred in both controls and patient specimens. The revised setpoints or revised values for controls and its clinical significance were communicated to the customers via Reagent Bulletins in April 2002, March 2004, November 2004. Another communication regarding low recovery of Precinom U/Precinorm U Plus controls was communicated in May 2006. Total Bilirubin: Roche Diagnostics has re-evaluated the assignments for the Total Bilirubin assays and has adjusted the C.f.a.s calibrator setpoints for both methods available on the COBAS INTEGRA and Roche/Hitachi analyzers. This change was triggered by internal investigation and customer feedback. The Roche Diagnostics US Standardization laboratory has reassigned the values based on a new procedure which maintained the same traceability to the Doumas method. The results were verified by using US reference laboratory. The revised setpoints or revised values for controls were communicated to the customers via a Reagent Bulletins in August 2006.
Proposed Labeling	Proposed labeling sufficient to describe the device, its intended use, and the directions for use can be found in Section V. We believe the proposed version of the device labeling presented contains all of the technical information required per 21 CFR 809.10.
Validation and Design Control	Development activities were conducted under appropriate design control procedures and the overall product specifications were met. The Declaration of Conformity with Design Controls and Results of Risk Analysis are provided in Section 5.1. Analytical Performance.
Confidentiality	Roche Diagnostics Corporation requests that the FDA not disclose the nature or existence of this submission until the substantial equivalence decision has been reached.

Closing

Modification of the Bilirubin Direct and Total reagents does not affect the intended use or indications for use of the device as described in the labeling, nor does it alter the fundamental scientific technology of the device. Therefore, we trust the information provided in this Special 510(k) will support a decision of substantial equivalence of the Bilirubin Direct and Total to their predicate.

If you have any questions or require further information, please do not hesitate to contact this office.

- Phone: (317) 521-3831
- FAX: (317) 521-2324
- email: corina.harper@roche.com

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Corina Harper, Regulatory Affairs Consultant
Roche Diagnostics Corporation
9115 Hague Road
Indianapolis, IN 46250

DEC 2 2 2006

Re: k063543
Trade/Device Name: COBAS Integra Bilirubin Direct
COBAS Integra Total Bilirubin Special
Roche/Hitachi Bilirubin Total
Regulation Number: 21 CFR 862.1110
Regulation Name: Bilirubin (total or direct) test system
Regulatory Class: Class II
Product Code: CIG
Dated: November 22, 2006
Received: November 24, 2006

Dear Ms. Harper:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (240) 276-0490. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address at http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Jean M. Cooper, M.S., D.V.M.

Jean M. Cooper, M.S., D.V.M.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K063543

Device Name:

COBAS INTEGRA Bilirubin Direct
COBAS INTEGRA Total Bilirubin Special
Roche/Hitachi Total Bilirubin

Indications For Use:

COBAS INTEGRA Bilirubin Direct

The cassette COBAS INTEGRA Bilirubin Direct (BIL-D) contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative determination of the direct (conjugated) bilirubin concentration in serum and plasma (test BIL-D, 0-049).

COBAS INTEGRA Total Bilirubin Special

The COBAS INTEGRA Total Bilirubin Special (BILTS) cassette contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative determination of total bilirubin in serum and plasma of adults and neonates (test BILTS, 0-985).

Roche Hitachi Total Bilirubin Special

For the quantitative determination of total bilirubin in serum and plasma of adults and neonates on Roche/Hitachi automated clinical chemistry analyzers.

Measurement of the levels of bilirubin and organic compound formed during the normal and abnormal distruction of red cells, if used in the diagnosis of liver, hemolytic hemoatological, and metabolic disorders, including hepatitis and gall bladder block

Prescription Use __XXX__ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off

Office of In Vitro Diagnostic Device
Evaluation and Safety

K063543